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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/032,214	12/20/2001	Juha Punnonen	0169.410US	4252

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EXAMINER	
OUSPENSKI, ILIA I	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 04/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/032,214	PUNNONEN ET AL.	
	Examiner	Art Unit	
	ILIA OUSPENSKI	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *321-350* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *321-350* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 02/10/2005, is acknowledged.
Claim 335 has been amended.
Claims 321 – 350 are pending.

2. Applicant's response to Species election requirement in the reply filed on 02/10/2005 is acknowledged. The traversal is on the ground(s) that the positions of amino acid substitutions set forth as different species are in fact identical.

The Species election requirement is withdrawn in view of Applicant's argument and amendment.

Claims 321 – 350 are under consideration in the instant application.

3. Sequence compliance: Applicant's amendment to the specification, filed 05/13/2002, appears to place the instant application in sequence compliance for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

4. Applicant's claim for domestic priority under 35 U.S.C. 119(e) and 120 is acknowledged.

However, the priority application USSN 09/888,324 fails to provide adequate support under 35 U.S.C. 112 for claims 321 – 250 of this application. Specifically, insufficient support was identified for the limitation of "a polypeptide sequence that differs from the polypeptide sequence of the extracellular domain of the wild-type primate B7-1 by at least one amino acid, and which comprises the substitution of an amino acid other than alanine at an amino acid residue position corresponding to

position 65 of the polypeptide sequence of wild-type human B7-1." Consequently, the claims have been accorded the priority of the filing date of the instant application, i.e. 12/20/2001.

Should Applicant disagree with the Examiner's factual determination above, it is incumbent upon Applicant to provide a showing that specifically supports the instant claim limitations.

5. Applicant's IDS, filed 03/28/2003, is acknowledged, and has been considered.

6. The use of trademarks has been noted in this application (e.g. FLAG on page 219). Each letter of the trademarks should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

7. 35 U.S.C. § 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

8. Claims 321 – 341 and 348 – 350 are rejected under **35 U.S.C. 101** because claimed invention is directed to non-statutory subject matter.

The claims, as presently recited, do not sufficiently distinguish over polypeptides as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products.

The claims are drawn to a polypeptide variant of an extracellular domain of a wild-type primate B7-1 comprising a polypeptide sequence that differs from the polypeptide sequence of the extracellular domain of the wild-type primate B7-1 by at least one amino acid, and which comprises the substitution of an amino acid other than alanine at an amino acid residue position corresponding to position 65 of the polypeptide sequence of wild-type human B7-1. The specification on page 45 defines a "variant" of a polypeptide as a polypeptide that differs in one or more amino acid residues from a parent or reference polypeptide, usually in at least about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acid or more residues. Therefore, there is no upper limit on the number of amino acid differences, nor is there a requirement that the "variant" itself be a B7 molecule or of primate origin. *Therefore, the claims as presently recited read on any polypeptide which does not have an alanine or a tyrosine (found in wild-type human B7-1) at position 65, including naturally occurring polypeptides.*

In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See Diamond v. Chakrabarty, 447 U.S. 303, 206 USPQ 193 (1980). Amending the claims to recite an "isolated" or "recombinant" polypeptide variant, as e.g. in claim 342, would be remedial in overcoming this rejection. See MPEP 2105.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 321 – 350 are rejected under **35 U.S.C. 112, first paragraph**, because the specification, while being enabling for a polypeptide variant of an

extracellular domain of a wild-type primate B7-1 comprising a polypeptide sequence that differs from the polypeptide sequence of the extracellular domain of the wild-type primate B7-1 by specifically defined amino acid substitutions, does not reasonably provide enablement for a genus of polypeptide variants of an extracellular domain of a wild-type primate B7-1 comprising a polypeptide sequence that differs from the polypeptide sequence of the extracellular domain of the wild-type primate B7-1 by at least one amino acid, and which comprises the substitution of an amino acid other than alanine at an amino acid residue position corresponding to position 65 of the polypeptide sequence of wild-type human B7-1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not provide a sufficient enabling description of the claimed invention.

The specification discloses a number of B7-1 variants which differ from wild-type human B7-1 by specific amino acid substitutions (e.g. Figure 2), and have varying binding affinities to CTLA-4 and CD28. As discussed in detail above in section 8, the claims as presently recited encompass in their breadth any polypeptide which does not have an alanine or a tyrosine at position 65. In the absence of a defined common structure that must be maintained by the members of the genus, the claimed invention is not described in such a way as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

Peach et al. (of record, IDS) teach that most single amino acid substitutions in B7-1 lead to abrogation of its binding to CTLA-4 and CD28 (see entire document, in particular, e.g. Table 1 at page 21184). Therefore it is unpredictable if any functional activity will be shared by polypeptide variants differing from wild-type B7-1 by amino acid substitutions that are not specifically defined.

In view of this unpredictability, the skilled artisan would not reasonably expect a polypeptide variant differing from wild-type B7-1 by amino acid substitutions that are not specifically defined to share the same functional properties the disclosed variants. The limitation regarding the CTLA-4/CD28 binding affinity ratio (e.g. claim 326) is not seen as providing the requisite specificity, because there is insufficient guidance to direct the skilled artisan to those amino acid substitutions which are essential for the disclosed activities.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary, the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

11. Claims 327, 340, and 347 are rejected under **35 U.S.C. 112, first paragraph**, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not provide a sufficient enabling description of the claimed invention.

The specification discloses B7-1 polypeptide variants which induce less T cell proliferation compared to wild-type B7-1 when used to costimulate T cells in soluble anti-CD3 induced proliferation assays (e.g. page 220 bottom paragraph).

A person of skill in the art is not enabled to make and use polypeptide variants which induce less T cell proliferation compared to wild-type B7-1 in the absence of primary T cell activation stimuli such as anti-CD3 antibodies, because it was well known

in the art at the time the invention was made that B7 molecules do not induce appreciable proliferation of T cells in the absence on primary T cell activation stimuli (see e.g. Linsley et al.,1996, US Patent 5,580,756; see entire document, in particular, e.g. Table 2 at column 32). Therefore, Applicant does not provide a sufficiently enabling disclosure regarding how to make and use the generically recited B7-1 polypeptide variants which induce less T cell proliferation compared to wild-type B7-1.

In view of the lack of predictability of the art to which the invention pertains and the lack of established protocols for assessing B7-induced T cell proliferation in the absence of primary T cell activation stimuli, undue experimentation would be required to make and use the claimed polypeptides with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed polypeptides are capable of inducing less T cell proliferation compared to wild-type B7-1 in the absence of primary T cell activation stimuli such as anti-CD3 antibodies.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 321, 323, 335, 337, 342, 344, 348, and 335 are rejected under **35 U.S.C. 102(b)** as being anticipated by Knauf et al. (US Patent No. 5,475,099; see entire document).

It is noted that the instant claims read on any polypeptide which does not have an alanine or a tyrosine at position 65, as discussed in detail in section 8 above.

Knauf et al. teach an isolated polypeptide, SEQ ID NO:52, which has a glycine (i.e. not an alanine or a tyrosine) at position 65 (see sequence listing at columns 99 – 102), and compositions comprising the polypeptide.

Thus the reference teachings anticipate the instant claimed invention.

14. Claims 321 – 323, 327, 329 – 331, 333, 335 – 337, 342 – 344, 348, and 350 are rejected under **35 U.S.C. 102(b)** as being anticipated by Freeman et al. (2000, US Patent 6,084,067; see entire document).

Freeman et al. teach a costimulatory polypeptide, B7-2, which has a phenylalanine at position which corresponds to position 65 of wild-type human B7-1, as evidenced by the attached alignment (see entire document, e.g. the Abstract), as well as B7-2 fusions with Ig polypeptides (e.g. columns 66 – 67). Freeman et al. further teach that B7-2 polypeptides are dimers (e.g. column 27 lines 5 – 11). Freeman et al. also teach that B7-2 induces less proliferation of T cells than wild-type B7-1 in a costimulation assay (e.g. columns 67 – 68 and in particular Figure 23, compare bars CHO/B7-1 and CHO/B7-2).

Thus the reference teachings anticipate the instant claimed invention.

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent

and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims 321 – 350 are provisionally rejected under the judicially created doctrine of **obviousness-type double patenting** as being unpatentable over claims 259 – 301, 368, 382 – 391 of copending Application USSN 09/888,324, and claims 259, 269 – 273, 306 – 308, and 332 – 3338 of copending Application USSN 10/479,901.

While the instant and copending claims do differ in certain structural (e.g. amino acid substitutions) and functional characteristics (e.g. CD28/CTLA4 binding affinity ratio), the instant and copending claims appear to be drawn to the same or nearly the same B7 molecules.

Applicant is invited to indicate whether or not the differences between the instant and copending claims are obvious in the interest of compact prosecution.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

17. Conclusion: No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is 571-272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ILIA OUSPENSKI
Patent Examiner
Art Unit 1644

April 4, 2005

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